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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/503,758	02/14/00	THILLY W	2

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021005
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EXAMINER	
STRZELECKA	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/503,758	THILLY, WILLIAM G.	
	Examin r	Art Unit	
	Teresa E Strzelecka	1656	

-- Th MAILING DATE of this communication appears on the cover sh t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *1-22,24,29-32 and 34-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25-28,33,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 23, 25-28, 33, 59 and 60 in Paper No. 12 is acknowledged.

2. Claims 1-22, 24, 29-32 and 34-58 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Groups I, III-XIV, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

Specification

3. A substitute specification will be required in case of allowance, pursuant to 37 CFR 1.125(a) because of numerous typing errors, inconsistently used subscripts, lack of explanations of terms used in equations, format of the equations, improper notation used for amino acids, etc. Some examples:

A) Throughout the specification "Point mutation" is used even in the middle of sentences.

B) Throughout the specification: inconsistent use or lack of use of subscripts, e.g. r_A and rA, F_h and Fh are used side by side.

C) Eqn. 3, page 35: no identification of symbols used in the equation.

D) Page 69, lines 1-8: E_h not defined; reference to Fig. 10 unclear, since what is described is not presented in Fig. 10.

E) Page 70, lines 3, 8, 18: $G{\cdot}E_h$ is shown in Fig. 14 in four variations, but not in the description on lines 3-18.

F) Eqns. 14-18: subscripts are larger than main characters.

G) Page 78, lines 18-24 and page 79, lines 1, 2, 11, 18: use of OBS^R and OBSR, both terms undefined.

H) Accepted amino acid notation is, e.g., "Pro" for proline, not "pro".

I) Suggestion to simplify the equations: instead of using e^x format, where x is usually a complex function, using exp(x) would greatly increase the clarity of the equations.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 23, 25-28, 33 and 59 rejected under 35 U.S.C. 102(a) as being anticipated by Tomita-Mitchell et al. (Gene vol. 223, pp. 381-391, November 26, 1998).

Tomita-Mitchell et al. teach a method for identifying a gene carrying a harmful allele by comparing the frequencies of point mutations (single nucleotide polymorphisms, SNPs) in the populations of young (newborn), proband (affected with the disease) and aged

(centenarian) individuals. The harmful allele is characterized by decreased frequency in the aged population and increased frequency in the proband population relative to the newborn population. Tomita-Mitchell et al. describe a case of point mutations present in a gene (or genes) creating a risk for pancreatic cancer. They determined age-dependent decline of deaths from pancreatic cancer and compared it with the theoretical prediction of the age-dependent decline and found an agreement between the two functions. The point mutation can be detected at a level of 10^{-6} by obtaining samples from general US populations of newborns and centenarians and using constant denaturant capillary electrophoresis (CDCE) combined with high-fidelity PCR to determine SNPs in these populations (Abstract; p. 381-384; Fig. 1, 2; Table 1, 2; page 389).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tomita-Mitchell as applied to claim 25 above, and further in view of Khrapko et al. (1) (Nucl. Acids Res. Vol. 25, pp. 685-693, 1997) and Khrapko et al. (2) (Nucl. Acids Res. Vol. 22, pp. 364-369, 1994).

A) Claim 60 is drawn to identifying point mutations by amplifying a region of a target gene from a pool of DNA fragments isolated from a population, melting and reanneling the PCR products to form a mixture of homo- and heteroduplexes containing point mutations, separating homo- from heteroduplexes and recovering heteroduplexes, amplifying the heteroduplex fragments to produce homoduplex wild-type DNA and homoduplex DNA

containing the point mutations, resolving and recovering the DNAs which contain point mutations and sequencing the DNAs to identify the point mutations.

B) Tomita-Mitchell et al. teach using constant denaturant capillary electrophoresis (CDCE) combined with high-fidelity PCR to determine SNPs in DNA samples from populations, but do not specifically teach the method steps of claim 60.

C) Khrapko et al. (1) teach a method of determining point mutations in a DNA sample at a fraction of 10^{-6} or above using constant denaturant capillary electrophoresis (CDCE) combined with high-fidelity PCR. The method comprises the following steps:

a) restriction digest of DNA isolated from cells to obtain a 200 bp DNA fragment with low temperature and high temperature isomelting domains,

b) enrichment of mutant sequences by constant denaturant gel electrophoresis (CDGE),

c) high fidelity PCR amplification resulting in fluorescently labeled products, using *Pfu* polymerase, which has an error rate of $2x10^{-6}$ errors per base per doubling,

d) separation of PCR heteroduplexes from homoduplexes by CDCE and collection of the heteroduplxes,

e) another round of high fidelity PCR in which mutant heteroduplexes are converted into homoduplexes by stopping the PCR reaction when the molar amount of unused primers still exceeds the molar amount of the products,

f) another round of CDCE separation of the homoduplexes,

g) isolation and sequencing of the mutants. (Fig. 1; page 686-689).

Khrapko et al. (2) teach that prior to CDCE separation the DNA fragments are boiled and reannealed, resulting in a mixture of homoduplexes and heteroduplexes, which are then

separated based on the differences in their melting temperature in a CDCE capillary column (page 365, paragraphs 6-9; page 366; Fig. 3, 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the point mutation detection method of Khrapko et al. (1) and (2) in the methods of Tomita-Mitchell et al.. The motivation to do so, expressly provided by Tomita-Mitchell et al., would have been that combining CDCE with high fidelity PCR permitted measurement of SNPs in large populations (up to 10^4 individuals) in a single experiment.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
August 23, 2001 TS

Kenneth R. Horlick, Ph.D.
KENNETH R. HORLICK
PRIMARY EXAMINER
GROUP 1800 8/23/01